EARLY LIFE EXPOSURES AND THE OCCURRENCE AND TIMING OF HEART DISEASE AMONG THE OLDER ADULT PUERTO RICAN POPULATION*

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*Few studies have examined the effects of early life conditions on the timing of the onset of heart disease. We use the remarkable example of a representative sample of the population of older Puerto Ricans aged 60–74 who lived in the countryside during childhood (*n *= 1,438) to examine the effects of seasonal exposures to poor nutrition and infectious diseases during late gestation on the timing of the onset and the probability of ever experiencing adult heart disease. Cox and log logistic hazard models controlling for childhood conditions (self-reported childhood health status and socioeconomic status [SES], rheumatic fever, and knee height) and adult risk factors (adult SES, obesity, smoking, exercise, and self-reported diabetes) showed that the risk of onset of heart disease was 65% higher among those born during high-exposure periods compared with unexposed individuals. However, there were no significant differences in median time of onset for those ever experiencing heart disease. As a comparison, we found that there were no significant seasonality effects for those who lived in urban areas during childhood. We conclude that early exposures in utero have important ramifications for adult heart disease among the older Puerto Rican population. We show, however, that while exposure is associated with the probability of ever experiencing adult heart disease, it is not associated with the timing of onset among those who do experience it.*

A growing literature suggests different mechanisms and pathways by which early life conditions can negatively impact older adult health, but the debate continues regarding the importance and magnitude of effects due to poor nutritional environment in utero relative to other events occurring throughout childhood and the life course. Several studies have shown the association between low birth weight—a reflection of fetal growth—and adult health outcomes (Gluckman and Hanson 2006; Newnham and Ross 2009). However, the hypothesis proposed by Barker (1998) regarding the importance of in utero nutrition remains controversial primarily because birth weight is a crude measure of fetal growth and there may be different ways to achieve a similar birth weight (Barker 2001). Important background conditions that influence early growth and development could also have independent effects on later health and mortality (Huxley, Neil, and Collins 2002; Joseph and Kramer 1996). Factors such as poor childhood socioeconomic status (SES) and poor childhood health can have substantial impacts on adult health (Davey Smith and Lynch 2004; Elo and Preston 1992; Gunnell et al. 1998; Hertzman 1994; Lundberg 1991; Wadsworth

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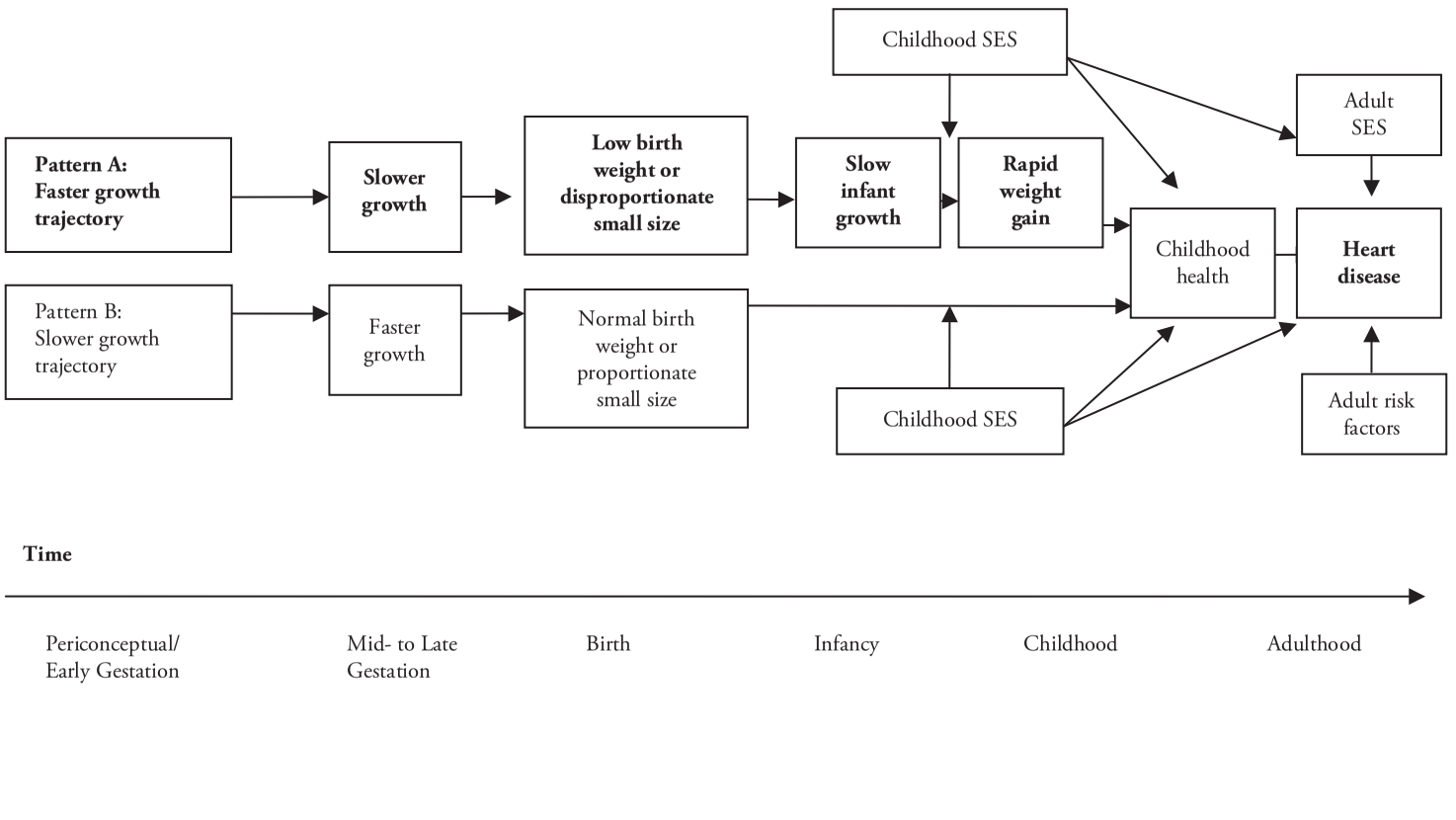
and Kuh 1997). Failing to control properly for these conditions will inflate the association between a valid indicator of early growth and adult health and mortality.

The Barker hypothesis has especially relevant implications for the developing world, where heart disease, for example, is projected to increase dramatically in the future (Kinsella and He 2009; Murray and Lopez 1996). We do not know the degree to which interuterine growth restriction in early life is an important determinant of adult heart disease in these settings. In that regard, Barker's argument stresses the importance of different patterns of fetal growth. One of the most prevalent patterns of fetal growth in the Western world (Barker 2001) is one that results in disproportionate growth at birth (Figure 1, pattern A). During the periconceptual period or early gestation, the magnitude of fetal demand for nutrients and the trajectory of fetal growth are established (Barker 2005; Godfrey and Barker 2000). Fetal demand for nutrients is thought to be small until late in pregnancy, which is a period of rapid fetal growth and organ development (Barker 1995), and particularly sensitive to variation in the supply of nutrients (Gardiner 2007; Godfrey and Barker 2000). However, a more favorable nutritional environment in early gestation (Figure 1, pattern A) sets the fetus on a path of rapid growth with higher expected nutrient demands, which makes the fetus more vulnerable to undernutrition in late gestation. Undernutrition or malnutrition during this later period just before birth leads to slower growth, which can permanently affect organ development, generate disproportionate fetal growth, and result in small size at birth. The combination of small size at birth and subsequent slow infant growth and/or exposure to more abundant nutrition leading to rapid weight gain in childhood increases the susceptibility to later adult disease and raises the risk of adult heart disease (Barker et al. 2002; Eriksson et al. 2001; Osmond and Barker 2000; Osmond et al. 1993). Barker's argument maintains that living conditions may alter the risk of disease, or conversely that slow early growth may increase vulnerability to the effects of poor living conditions, but poor living conditions are not an important confounding factor (Barker et al. 2001) and rather may add to the effects of early life conditions (Barker 1995). Adult lifestyle (smoking, alcohol intake, and obesity) has also been shown to be independent from associations between birth weight and adult blood pressure (Godfrey and Barker 2000).

A different pattern of fetal growth also resulting in disproportionate growth is invoked within the Barker framework. A fetus exposed to poorer nutrition in early gestation (Figure 1, pattern B) has a slower trajectory of growth and is thus less vulnerable to maternal undernutrition during late gestation (Barker 2005). The slow-growing fetus and eventually the infant and young child are still susceptible to the effects of exposure to a more abundant nutritional environment. However, the differential effects of timing (during late gestation, early infancy, childhood) of this kind of exposure are still largely unknown. If exposure to better nutrition occurs in late gestation, birth size may be larger or even closer to normal size (Painter et al. 2006; Roseboom et al. 2000). Indirect evidence of the Barker hypothesis suggests that a slower-growing fetus may be able to recover in late gestation and live longer (Doblhammer 2004). In contrast, recent evidence suggests that health problems may later occur (Painter et al. 2006; Roseboom et al. 2000). If the slow-growing fetus continues to be exposed to undernutrition during late gestation, a small (probably more proportionately sized) baby is born, and exposure to more nutritional abundance in infancy or early childhood can result in similar types of problems as those associated with pattern A (Figure 1).

The most direct evidence for the effects of nutrition during a particular gestational period comes from studies conducted on the Dutch Famine, in which famine conditions were sufficiently short in duration to allow a more clear delineation of specific gestational periods (Painter et al. 2006; Ravelli et al. 1998; Roseboom et al. 2000). These studies suggest that the timing of nutritional insults during pregnancy have different effects for different health outcomes. Thus, individuals exposed to famine during late gestation show impaired glucose tolerance as adults (Ravelli et al. 1998), an example of fetal growth pattern A (Figure 1); those exposed to famine during early gestation show a

Figure 1. Two Different Patterns of Fetal Growth and Pathways to Heart Disease Influenced by Nutrition Using the Barker Hypothesis



higher prevalence of heart disease (Roseboom et al. 2000) and early onset of heart disease (Painter et al. 2006), an example of fetal growth pattern B (Figure 1). Nevertheless, the sample sizes for these studies have been small, and other famine studies have shown weaker or no associations between undernutrition in utero and later adult health (Kannisto, Christensen, and Vaupel 1997; Stanner et al. 1997).

Abundant indirect evidence in the social sciences (demography and anthropology) and public health supports the fetal growth patterns presented in Figure 1 (Bengtsson and Lindstrom 2003; Costa 2005; Doblhammer 2004; Gavrilov and Gavrilova 2005; Mazumder et al. 2009; Moore et al. 1999). These studies used season of birth to capture the effects of marked seasonality of diet and disease within a community. Season of birth could be a suitable and ideal measure of early growth and development in population surveys under certain conditions because it captures the seasonality of food supply and is unrelated to family background variables such as SES (Doblhammer 2004). It is not a perfect indicator because other factors, such as differences among populations in immune functions and exposure to other infections or environmental risks, may be important (Gamble 1980; Guerrant, Lima, and Davidson 2000; Moore et al. 1999; Simondon et al. 2004). However, under some conditions (to be fully spelled out later), season of birth could be used in population surveys to disentangle the effects of substandard nutrition in utero from the effects of other childhood conditions (e.g., health, SES) and adult risk behavior on adult health status.

An important caveat is in order. So far we have used the notion of "nutritional status" as applied to mother or child as if it were unproblematic. Nothing could be further from the truth. Most of the literature linking poor fetal rates of growth and adult chronic disease says nothing about the nature of factors leading to poor nutrition. These can be very heterogeneous and may have very different implications for adult health and, more importantly, will almost surely alter the conditions under which our measures (season of birth among others) may be valid. The first factor is maternal nutritional status, which depends on two variables: (1) maternal supply, which is entirely dependent on the ability to access high-quality sources of nutrients; and (2) maternal demand for caloric intake, which is heavily dependent on the degree to which infectious and other diseases shore up metabolic requirements to maintain resistance and/or recovery functions at levels needed by the organism. On the fetal side, the same duality applies: conditional on maternal nutritional status, fetal nutritional status depends on supply and demand conditions. As in the case of the mother, the demand is a function of the disease environment to which the fetus is exposed. We know that infectious diseases may, by themselves, inflict damage with potential consequences for adult health. Thus, for example, it is thought that some infections early in life may lead to subsequent inflammation (Finch and Crimmins 2004) and to an overreactive immune system. However, these effects of an environment of infectious diseases are in addition to, not instead of, the effects generated by the influence of disease on nutritional demands.

The above qualification has nontrivial consequences for measurement and, in particular, for the interpretation of the effects of season of birth, our main instrument in this study. Originally, seasonality was thought to represent the supply side of nutritional status: in societies navigating a Malthusian low-technology landscape depending on seasonal crops for survival, the timing of pregnancy could arguably become a matter of life or death or of good or bad health in adulthood. However, in many societies exposed to sharp weather oscillations, alternating highly dry with highly rainy periods, seasonality could well spell a different scenario: rainy seasons are more propitious for an abundance of vectors that are carriers of infectious diseases. Even if there were no seasonality in the food supply, seasonality of weather patterns could induce cycles of high and low nutritional demand. From the point of view of a mechanism relating fetal nutritional status to adult chronic disease, it is immaterial whether seasonality is punishing because of its impact on the supply of nutrients (keeping constant demand) or because of its effect on the demand of nutrients (keeping constant supply).

Overall, studies using season of birth have found that being born during or right after a harvest, when nutritional supplies are more plentiful, is associated with longer life. Because of the wide variation in nutritional abundance, those born after the harvest would have been exposed at conception to leaner times (Figure 1, pattern B), and those born after a lean period would have been exposed at conception to better nutritional times (Figure 1, pattern A). Thus, Union Army veterans between 60 and 74 years old in 1900 and born in the second or third quarter (after leaner times) relative to the fourth quarter (after the harvest) did not live longer (Costa 2005). U.S. birth cohorts from the late 1880s showed that those born in April–June (the time before the harvest) lived shorter lives than those born in October–November (Gavrilov and Gavrilova 2005). Those born during the spring and summer in the 1800s in four rural parishes in southern Sweden experienced higher mortality risks than those born in the fall (Bengtsson and Lindstrom 2003). Examining deaths from more recent times (1968, late 1980s–1990s) of individuals aged 50 and older in Denmark, Austria, Hawaii, Australia, and the United States, Doblhammer (2004) found that individuals born after the harvest lived longer than those born after the lean period; this pattern held when cause-specific mortality for heart disease in the United States was examined. Recent studies from Gambia show that rural Gambians born in the nutritionally deprived hungry season (July–December) had higher mortality risks than those born in the harvest season (January–June) (Moore et al. 1999).

EARLIER HEALTH AND THE TIMING OF ONSET OF ADULT CHRONIC CONDITIONS

The bulk of research on effects of early conditions on adult illnesses focuses on the degree to which early exposure increases the risk of adult illnesses but is largely silent on the possibility that exposure could also affect the *timing of onset* of such illnesses (Barker et al. 2002; Eriksson et al. 2001; Gardiner 2007; Gluckman and Hanson 2006; Osmond et al. 1993) with only a few noted exceptions (e.g., Painter et al. 2006). It might be expected that smallness at birth because of already compromised fetal development combined with slow growth in infancy and later rapid growth in childhood might set the stage not only for higher risk of heart disease but also for earlier onset of heart disease. However, to date we have not had access to the necessary data to examine early onset of disease and nutrition during different periods of gestation because this requires knowledge of two elusive variables: the timing of the onset of disease and nutrition during different gestational periods. The recent exception is a study on early onset of heart disease (Painter et al. 2006), which suggests that growth retardation in utero may lead to early onset of heart disease and that the fetal growth pattern B (Figure 1) might be an important pathway. However, the sample size for this study was small, and thus the conjecture of a relation between early exposure and timing of onset of adult illnesses was not thoroughly put to the test.

The aim of this article is to test the degree to which there is an association between early conditions in utero and the timing of onset of heart disease by using a remarkable case study of older Puerto Ricans. Few studies have examined the present health of older Puerto Ricans, but our previous research shows that Puerto Ricans over age 60 in general have a higher prevalence of obesity (a risk factor for heart disease) but a lower prevalence of heart disease in comparison with mainland U.S. adults over age 60. We have also shown that early life conditions, especially poor early childhood health and rheumatic fever, help explain part of the variability of the prevalence of heart disease (Palloni et al. 2005). We also examined the effects of season of birth on adult heart disease on a subset of older Puerto Ricans who were born and lived during childhood in the countryside; we found a higher prevalence of heart disease among those born at the end of the lean season (McEniry et al. 2008). In this article, we extend this line of inquiry to examine whether season of birth also predicts early onset of heart disease and the possible reasons for any differences in patterns with the Dutch Famine studies (Painter et al. 2006; Roseboom et al. 2000).

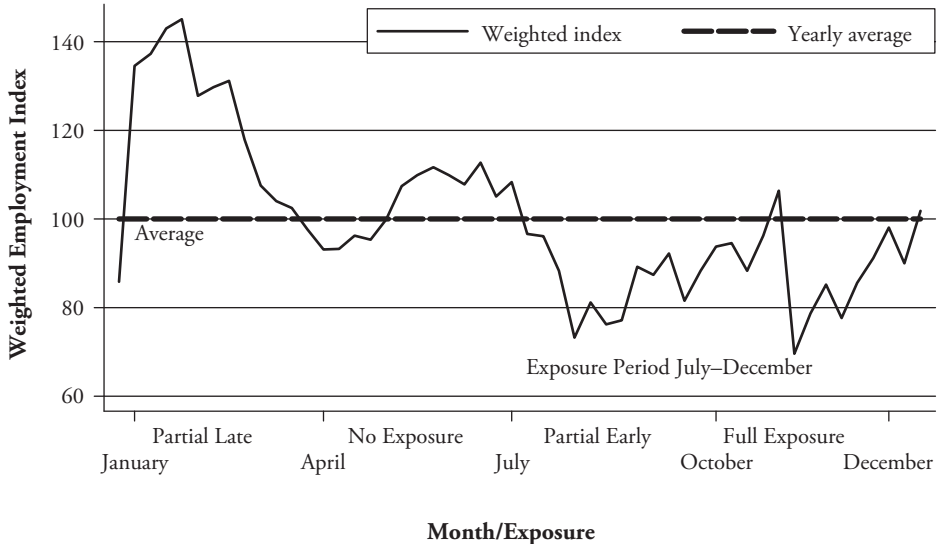
THE CASE OF PUERTO RICO

The population of older Puerto Rican adults born during the late 1920s to early 1940s presents a remarkable case study by which to examine the effects of early life exposures on adult heart disease. Puerto Ricans themselves present a unique mixture of U.S., Latin American, and Caribbean cultures, but the cohort of Puerto Ricans born in the late 1920s to early 1940s was unique in at least three important aspects. First, a large proportion of older adults born and raised in Puerto Rico in rural areas during this period were probably exposed to poor nutrition during pregnancy and early infancy due to social and economic circumstances during the late 1920s, when conditions in rural areas were precarious and when a large proportion of Puerto Ricans were unemployed or underemployed during extended periods of the year (Clark 1930). Second (and more importantly), by the late 1920s, sugarcane dominated the agricultural sector in Puerto Rico; and because this industry followed a very marked seasonal pattern for agricultural workers (Clark 1930; Gayer, Homan, and James 1938), wages, the single most important means to purchase food and have a proper diet, also followed a similar seasonal pattern (Figure 2). These circumstances make it more feasible to entertain hypotheses regarding the cyclical nature of early nutrition for rural Puerto Rican families. The cutting season occurred in the first half of the year (January–June), and rural families would have experienced better nutritional times due to both an abundance of provisions and adequate wages. This season was followed by a slack season lasting most of the second half of the year, when rural families would have experienced a less favorable nutritional environment. Third, the peak season for exposure to infectious and parasitic diseases also occurred during a relatively specific period during the second half of the year, coinciding with the hurricane season (August–October); this period brought heavy rains and flooding, which increased exposure to infectious and parasitic diseases such as malaria and dengue and created conditions that enhanced the transmission of bacterial diseases such as dysentery, cholera, and diarrhea (Rigau Pérez 2000). Increased exposure to seasonal infectious and parasitic diseases can augment the impact on nutritional status for both a mother and her fetus (Moore et al. 1999; Scrimshaw 1968, 1997). Thus, poor nutrition due to reduced purchasing power was complicated by exposure to infectious diseases, thus producing more negative environments for mothers, unborn children, and infants alike.

In our analysis, we focus on rural families because conditions in rural areas were precarious in Puerto Rico during the late 1920s to early 1940s and because our previous research shows no effects of seasonality in more urban areas (McEniry et al. 2008). Although we cannot elucidate the mediating mechanisms, we can eliminate competing hypotheses explaining the observed association. We hypothesize that late gestation (third trimester) is particularly important for nutritional deficiencies and that the highest and lowest risk of exposure for rural Puerto Rican families in the late 1920s to early 1940s was prior to the beginning of the sugarcane harvest (October–December) and toward the end of the harvest (April–June), respectively (Figure 2). We conjecture that the level of exposure during late gestation is associated not only with the risk of occurrence of heart disease but also with the timing of onset of heart disease. In particular, the timing of onset of heart disease should be earlier for those who were born toward the end of the lean season and who were completely exposed during late gestation to the period with worse conditions; the timing should be later for those born during seasons of abundance (close to the end of the harvest season), when there was no exposure during late gestation. Risks of contracting heart disease should also be higher for those born toward the end of the lean season and lower for those born during seasons of abundance.

This investigation is important for two reasons. First, because little research has examined the possibility that poor nutrition in utero also affects early onset of heart disease, it is thus uncharted territory that deserves more attention. Second, relatively little research has examined the merit of the Barker hypothesis among older adults in Latin America and

Figure 2. Seasonal Variation in Plantation Employment and Hypothesized Exposure During Late Gestation



Source: Clark (1930). Data are for sugar, tobacco, and coffee plantations, 1924–1926.

Notes: The figure is reprinted by permission from the *Journal of Gerontology*, where it was originally printed (McEniry et al. 2008). The graph depicts a composite employment index weighting the number of days worked in the three most important agricultural areas (sugarcane, coffee, and tobacco) by the number of laborers reported in these industries in the 1920s. Agricultural employment followed a cyclical pattern similar to that of the sugarcane industry, in which employment was highest during the first six months of the year and lowest during the later part of the year (Clark 1930).

the Caribbean, and Puerto Rico presents a unique case study with which to examine the hypothesis. The particular nature of the seasonal variation of nutrition in the Puerto Rican countryside during the late 1920s to early 1940s provides an opportunity to further examine the two widely prevalent patterns of fetal growth in the Western hemisphere (Figure 1). The Puerto Rican nutritional pattern for rural families was one in which those born at the end of the lean time (hypothesized to be a greater risk for adult heart disease) were exposed to more favorable nutrition conditions in early gestation (during the harvest period), whereas those born toward the end of the harvest (hypothesized to be a lower risk for adult heart disease) were exposed to less favorable nutrition in early gestation. Finally, relatively little research has shown the relative importance of in utero exposure to poor nutrition, other childhood conditions, and adult risk factors for adult heart disease. Our study attempts to do this by controlling for other childhood conditions and adult risk factors.

METHODS AND DATA

Data

The Puerto Rican Elderly: Health Conditions (PREHCO) project was designed to gather quality baseline data on issues related to the health of elderly Puerto Ricans (PREHCO 2007). The data collected offer a substantial amount of information within the limits permitted by face-to-face interviews in a cross section. PREHCO is a cross-sectional survey of the noninstitutionalized population aged 60 and over and their surviving spouses. The sample

is a multistage, stratified sample of the elderly population residing in Puerto Rico, with oversamples of regions heavily populated by people of African descent and of individuals over age 80. The data were gathered through face-to-face interviews with elderly adults, including those with cognitive limitations who required the presence of a proxy to provide information, and with their surviving spouses, regardless of age. The field work consisted of interviews conducted with a laptop and specialized anthropometric measurement and physical performance. More than 20,600 households were visited in 233 sample sections. A total of 4,293 in-home face-to-face target interviews were conducted between May 2002 and May 2003, and second-wave data were collected during 2006–2007. In addition, 1,444 spouses were interviewed during the first wave, 1,043 of them aged 60 or older. The percentage of interviews requiring a proxy was 12.4%. Only 4.7% refused to participate, and the overall response rate was 93.9%. The questionnaire included modules on demographic characteristics, health status and conditions, cognitive and functional performance, labor and economic status, income and assets, health insurance and use of health services, family structure, intergenerational transfers, housing, anthropometric measurements, and physical performance. Despite the very high response rate, an analysis of nonrespondents was conducted, but no significant differences were found between those who responded and those who did not respond.

Measures

Prenatal exposures. We defined seasonal exposure to poor nutrition and infectious diseases based on birth quarter and the months of the slack or lean season (July–December) in the Puerto Rican sugarcane industry (Clark 1930; Gayer et al. 1938). The peak season for infectious diseases such as malaria also occurred during this period (Rigau Pérez 2000). Mid- to late gestation and early infancy may all be sensitive times to poor nutrition. However, we began with the supposition that late gestation is most relevant. Based on this assumption, we identified different levels of exposure according to the degree of overlap between the third trimester of gestation calculated from the report of month of birth and the months of the slack season defined above. *Full exposure* (fourth quarter of birth) means that the third trimester fell completely within the slack period. *Partial exposure* means that the third trimester of gestation fell partially within the window defined by the slack months, either early (third quarter) or late (first quarter). *No exposure* during the third trimester was reserved for those whose third trimester of gestation fell completely out of the window of slack months. Dummy variables were created to represent these levels of exposure, with the reference group being the *no exposure* group.

Childhood conditions. To assess childhood conditions, we used retrospective questions on childhood health and childhood SES and anthropometric measurement of knee height. Respondents were asked to rate their childhood health using a five-point scale: "Would you say that your health as a child was excellent, very good, good, fair, or poor?" This type of self-reported childhood health has good reliability in the developed world and has been associated with indicators of poor intrauterine development (Haas 2007). In addition, these self-reports are quite consistent across the two waves of the PREHCO study, and their changes are not associated with changes in self-reported conditions or health. If the effects of poor early exposures in utero are confounded with childhood health, and if season of birth is an adequate measure of in utero nutritional experiences, then we should be able disentangle the effects of childhood health.

There is no consensus in the literature regarding the definition and use of these variables. However, in our study, we were most interested in the effects of poor childhood health. Thus, we created a dichotomous variable for poor childhood health, where 1 indicated that the respondent rated their health during childhood as poor and 0 indicated all other responses. Poor childhood socioeconomic status was classified as either with or without formal education using self-reports of father's education. The occupation of the respondent's father

was self-reported and classified as either agricultural or not according to the international standard classification of occupations (International Labor Organization 2004).

Knee height was measured in the home of the respondents. We used gender-specific quartiles of knee height as a proxy for early stunting (Eveleth and Tanner 1990). Knee height is thought to be particularly sensitive to nutritional status during childhood (Leitch 1951), although there is no consensus regarding its definition for adults and it has not been frequently measured in population surveys. In the anthropometric literature, height is often measured using quartiles (Gunnell et al. 1998). Thus, we used quartiles of knee height and defined gender-specific dichotomous variables, where 1 indicates the lowest quartile of knee height and 0 indicates all other quartiles.

Adult risk factors. Major adult risk factors for heart disease (Kuh and Ben-Shlomo 2004) were measured: (1) body mass index (BMI) was calculated from weight and height measurements as weight in kilos divided by height in meters squared, and then classified as obese if BMI was greater than or equal to 30; (2) respondents who ever smoked were identified through their responses to survey questions about whether they had smoked more than 100 cigarettes in their lifetime; (3) individuals who exercised were identified according to responses about whether they had done strenuous exercise on a regular basis during the past 12 months; (4) diabetes was defined as a dichotomous variable based on respondents' answers to questions about whether a doctor had ever diagnosed them with diabetes; and (5) respondents' assessment of number of years of schooling was used to identify highest level of education as primary versus higher levels of educational attainment.

Timing of heart disease. Respondents experienced the event (heart disease) if they answered affirmatively to a question about whether a doctor had ever diagnosed them with heart disease. We defined time at onset of heart disease as the respondents' self-reported age and included those with an age of onset of at least 40 years (this excluded only 21 respondents, and we found no difference in the analysis after we later included them). We rescaled the time of onset of heart disease to start at 0 by subtracting age of diagnosis from age 40 for respondents with heart disease and subtracting current age from 40 for respondents without heart disease. We evaluated irregularities and heaping by examining a plot of the frequency distribution of the estimated age of onset. Graphical results showed no evidence of systematic errors (results not shown). They reflect only noise and a tendency to round off digits, but even these distortions are of minor consequence and, if anything, should only lead to attenuation of estimated effects.

Models and Estimation

Imputation. In an effort to include all relevant cases we used multiple imputation procedures (Raghunathan, Reiter, and Rubin 2003; Rubin 1987; Schafer 1997; Van Buren, Boshuizen, and Knook 1999) implemented in IVEware (Raghunathan, Solenberger, and Van Hoewyk 2007) on the entire sample of PREHCO respondents. For details on the imputation procedure, see the appendix.

Subsample for estimation. We selected a subsample of elderly who stated that they were born in Puerto Rico and who responded affirmatively to a survey question that asked them if they had lived for a prolonged period of time in the countryside prior to the age of 18 (n = 1,438 out of 4,293). The rural population was at a considerably higher risk for poor nutrition than the urban population during the 1920s to early 1940s (Clark 1930). A high percentage of respondents were born in Puerto Rico (97%). We hypothesize that those who lived in the country as a child had the highest risk of exposure to deficient prenatal nutrition while also being exposed to infectious diseases. Ignoring rural-urban differences and estimating effects on the entire samples would underplay the role of weather seasonality. In addition, we selected respondents aged 60–74 to generate estimates for the subpopulation that was most at risk of having been affected by harsh early childhood experiences and that simultaneously had larger probabilities of surviving due to their exposure to the massive

deployment of medical technologies and public health measures during the period after 1930 (Palloni et al. 2005). Thus, this cohort may be able to provide us with some insights into whether early childhood experiences are important in later life since it is less affected by mortality-driven selection than the group of cohorts who preceded them (those aged 75 and older). To provide a telling contrast, we also estimated our models in the subsample of those born in more urban areas in Puerto Rico (n = 1,128 out of 4,293).

Estimation. We estimated Kaplan-Meier survival, hazard, and cumulative hazard functions and employed the log rank test to test statistical differences between survival curves. This was done separately for the subsamples of individuals who spent long periods of time under age 18 in rural areas and those who did not. We also estimated models including cases in which respondents indicated that onset of heart disease began before the age of 40. Median age of onset for those who experienced heart disease was computed using Kaplan-Meier survival analysis and was observed to be 60 in both subsamples. We estimated the effects of level of exposure on the timing of heart disease through a series of Cox regression models as well as through models in which we parameterized the baseline hazard with a log logistic regression. This was done since the Nelson-Aalen estimator of the hazard risk suggested strong nonmonotonicity with duration of exposure.[1] Standard tests assessed the adequacy of model fit and assumptions: (a) Cox-Snell residuals to test for the overall fitness of models, and least square regression to describe the slope and y-intercept of plots of Cox-Snell residuals and Nelson-Aalen estimator hazard estimates; (b) plots of log-log of survival against the natural log of time to test the proportional hazards assumption of the Cox model; and (c) plots using natural log of the cumulative hazard from the Nelson-Aalen estimator to test appropriateness of the log logistic model (Klein and Moeschberger 1997). We calculated predicted values for the hazard and cumulative hazard. Because different gestational exposure can affect (1) the timing of onset of the disease and (2) the probability of ever experiencing the event, we carried out auxiliary tests to discriminate between these two mechanisms. The first was to compare the median time to the onset of the disease among those who actually experienced the event in the high- and low-exposure groups. The second was to compare the proportion who ever developed the disease across the same exposure groups.

RESULTS

General Characteristics of the Sample

The only variable among the selected variables of interest (Table 1) to show a statistically significant association with seasonal exposure was heart disease ($\chi^2(3) = 12.37$, $p = .0060$). Those who experienced full exposure during late gestation (fourth quarter) to poor nutrition and infectious diseases showed the highest prevalence of heart disease (23%). Those with partial exposure showed a lower prevalence of heart disease (18%, 15%), and unexposed individuals (second quarter) experienced the lowest prevalence of heart disease (11%). Examination of the distribution of self-reported age at diagnosis revealed no systematic biases generated by heaping or other types of distortions that are common with recall of the timing of events (results not shown). There were no statistically significant differences in prevalence of heart disease across season of birth for respondents who lived in urban areas during childhood (n = 1,128, results not shown).

1. We also estimated models testing for interactions between season of birth and infectious diseases (e.g., malaria, dengue) and father's agricultural employment, but we found no significant effects and thus do not report these models here. Finally, we estimated models without controls for knee height, but the results did not change and thus are not reported here.

Table 1. Characteristics of the Sample: Puerto Ricans Aged 60–74, 2002–2003

	Season of Exposure During Late Gestation				
Variable	Full Exposure: Born in October–December	Partial Late Exposure: Born in January–March	Partial Early Exposure: Born in July–September	No Exposure: Born in April–June	All Exposures
Demographic					
Female (%)	54	51	47	50	50
Age (years)	66 (4)	66 (4)	66 (4)	66 (4)	66 (4)
Childhood					
Poor health (%)	27	19	28	22	24
Rheumatic fever (%)	2	2	2	2	2
Knee height (cm)	46 (5)	46 (5)	47 (5)	46 (5)	46 (5)
Father no education (%)	46	44	39	48	44
Father worked in agriculture (%)	63	68	58	71	65
Adult Risk					
Obese (%)	25	31	27	28	28
Diabetes (%)	34	32	31	29	31
Ever smoked (%)	37	32	37	32	35
Exercises (%)	46	38	48	45	44
Primary education (%)	62	68	57	64	63
Heart disease (%)	23	18	15	11	17
Total Number	360	340	344	394	1,438

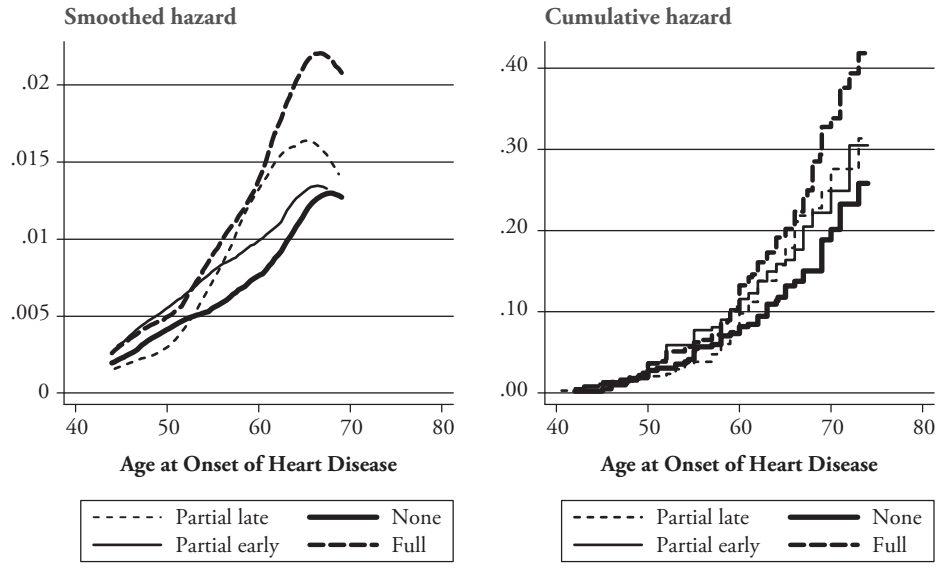
Source: PREHCO imputed and weighted (n = 1,438 from full sample of 4,293); all 60- to 74-year-olds who were born in Puerto Rico, lived in the countryside before age 18, and indicated that the onset of heart disease was at least at age 40.

Notes: The broad exposure period is July–December, and the level of exposure is based on the overlap between the third trimester of pregnancy and the lean harvest season: full exposure (fourth quarter), partial exposure (first quarter or third quarter), and no exposure (second quarter). Mean age and knee height are followed by standard deviations in parentheses. The distribution of births by seasonal exposure is displayed in the last row of the table.

Kaplan-Meier Estimates

A log rank test confirmed strong significant differences between the survival curves of time to diagnosis of heart disease by level of exposure ($\chi^2(3) = 8.91$, $p = .0306$). There were fewer events (diagnosis of heart disease) among unexposed persons than among those with complete exposure: the observed number of events among those exposed was 86, whereas the expected number was 68. Among the unexposed, the observed number of events was 55, and the expected number was 72. There was no difference between observed and expected frequencies in the other categories of exposure. The estimates of the smoothed hazard and cumulative hazard functions by quarter of birth suggest larger differences due to level of exposure after age 60 (Figure 3). The risk of developing heart disease in the group with full exposure during late gestation (fourth quarter) was approximately twice as high as for those within the unexposed category (second quarter) at later ages. The baseline hazard function showed a monotonic increase with age, peaking at around ages 65–67 and then decreasing. There were no statistical differences in survival curves by level of exposure for respondents who lived in urban areas during childhood (n = 1,128, results not shown).

Figure 3. Kaplan-Meier Hazard Estimates by Level of Exposure During Late Gestation



Source: PREHCO imputed (n = 1,438); 60- to 74-year-olds who were born in Puerto Rico and lived in the countryside as a child.

Multivariate Models: Simple Cox Models

Age- and sex-adjusted relative hazards for full exposure during late gestation and for childhood health and rheumatic fever using Cox regressions were 1.71 (95% CI: 1.22, 2.41), 1.38 (95% CI: 1.06, 1.79) and 2.69 (95% CI: 1.58, 4.58), respectively (Table 2, Models 1 and 2). Very similar relative hazards were obtained in a model including these variables simultaneously and then all covariates (Table 2, Models 3 and 4). The risk of reporting heart disease was 65% higher among those born with full exposure (fourth quarter) compared with unexposed individuals (second quarter). As expected, and confirming other findings in the literature (Elo and Preston 1992), early experience with rheumatic fever had the most powerful effects, more than doubling the risk of heart disease. The model was deemed appropriate by the Cox-Snell test, which suggested a high degree of fit.[2] A plot of the log-log of survival against the natural log of time adjusted for covariates produced parallel lines across level of exposure (quarter of birth); thus, the proportionality assumption of the Cox model was also deemed to be reasonable (results not shown). There were not statistically significant effects of seasonality on heart disease for respondents living in urban areas during childhood (n = 1,128, results not shown).

Multivariate Models: Log Logistic Models

Age- and sex-adjusted log logistic regression time ratio (TR) for full exposure during late gestation, childhood health, and rheumatic fever were 0.78 (95% CI: 0.67, 0.92), 0.86 (95% CI: 0.76, 0.98), and 0.61 (95% CI: 0.46, 0.81), respectively (Table 3, Models 1 and 2); these

2. Regression of the Cox-Snell residuals on the Nelson-Aalen estimates produced an R^2 of .98 with slope close to 1 (1.04) and y-intercept close to 0 (–0.01).

Table 2. Effects of Early Life Conditions and Adult Risk Factors on the Onset of Heart Disease, Using Cox Regression: Puerto Ricans Aged 60–74, 2002–2003

Variable	Model 1	Model 2	Model 3	Model 4
Demographic				
Female	1.08 (0.84, 1.37)	1.09 (0.85, 1.39)	1.09 (0.85, 1.39)	0.99 (0.76, 1.29)
Age 60–64	1.55 (1.09, 2.20)	1.52 (1.07, 2.16)	1.56 (1.10, 2.23)	1.62 (1.13, 2.31)
Age 65–69	1.41 (1.03, 1.91)	1.37 (1.01, 1.87)	1.41 (1.04, 1.93)	1.39 (1.02, 1.90)
Age 70–74 (ref. group)	1.00		1.00	1.00
Level of Exposure				
None (ref. group)	1.00			1.00
Partial early	1.31 (0.91, 1.88)		1.32 (0.92, 1.90)	1.32 (0.91, 1.90)
Partial late	1.34 (0.93, 1.92)		1.37 (0.95, 1.96)	1.33 (0.93, 1.92)
Full	1.71 (1.22, 2.41)		1.70 (1.21, 2.38)	1.65 (1.18, 2.33)
Childhood Conditions				
Poor health		1.38 (1.06, 1.79)	1.39 (1.06, 1.81)	1.36 (1.04, 1.78)
Rheumatic fever		2.69 (1.58, 4.58)	2.62 (1.54, 4.47)	2.45 (1.42, 4.22)
Low knee height				0.89 (0.67, 1.19)
Father no education				1.28 (0.98, 1.67)
Father in agriculture				0.94 (0.72, 1.23)
Adult Risk				
Obesity				1.65 (1.28, 2.13)
Diabetes				1.56 (1.21, 2.00)
Ever smoked				1.14 (0.87, 1.49)
Exercises				0.85 (0.65, 1.10)
Primary education				1.00 (0.76, 1.32)
Log-Likelihood	–1,824	–1,820	–1,815	–1,796
Number of Observations	1,438	1,438	1,438	1,438

Source: PREHCO imputed (n = 1,438 from full sample of 4,293); 60- to 74-year-olds who were born in Puerto Rico and lived in the countryside before age 18. The broad exposure period is July–December, and the level of exposure is based on the overlap between the third trimester of pregnancy and the lean harvest season: full exposure (fourth quarter), partial exposure (first quarter or third quarter), and no exposure (second quarter). In Model 4, omitting knee height produced similar results.

Notes: Numbers shown in the table are relative hazards; 95% confidence intervals are in parentheses.

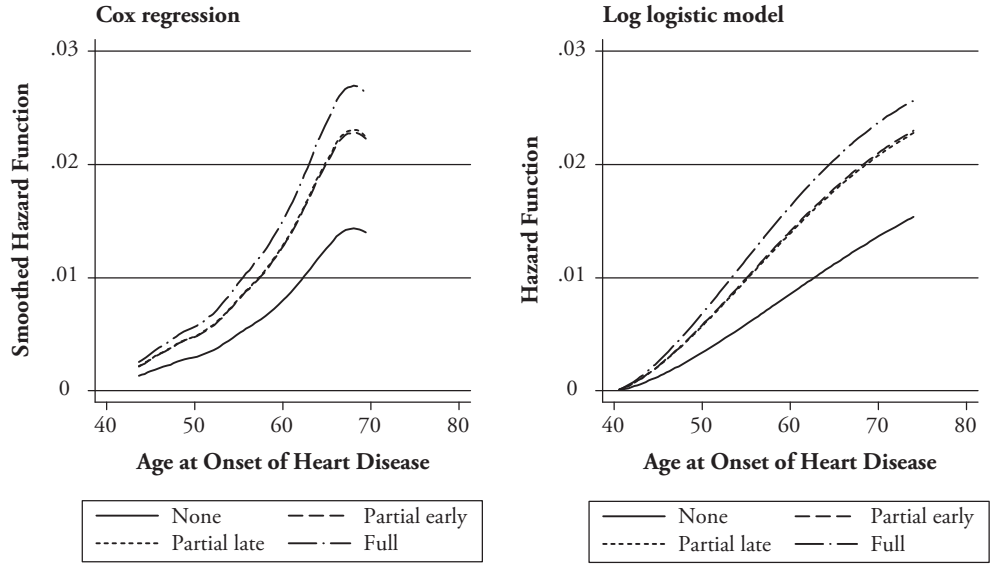
Table 3. Effects of Early Life Conditions and Adult Risk Factors on the Onset of Heart Disease, Using Log Logistic Models: Puerto Ricans Aged 60–74, 2002–2003

Variable	Model 1	Model 2	Model 3	Model 4
Demographic				
Female	0.97 (0.86, 1.08)	0.96 (0.86, 1.08)	0.96 (0.86, 1.08)	1.00 (0.88, 1.13)
Age 60–64	0.86 (0.74, 1.00)	0.87 (0.76, 1.01)	0.86 (0.75, 1.00)	0.85 (0.74, 0.99)
Age 65–69	0.89 (0.78, 1.00)	0.90 (0.79, 1.03)	0.89 (0.78, 1.02)	0.89 (0.78, 1.02)
Age 70–74 (ref. group)	1.00	1.00	1.00	1.00
Level of Exposure				
None (ref. group)	1.00		1.00	1.00
Partial early	0.88 (0.75, 1.04)		0.88 (0.74, 1.04)	0.87 (0.74, 1.03)
Partial late	0.88 (0.75, 1.04)		0.88 (0.74, 1.03)	0.88 (0.74, 1.04)
Full	0.78 (0.67, 0.92)		0.79 (0.68, 0.93)	0.79 (0.68, 0.93)
Childhood Conditions				
Poor health		0.86 (0.76, 0.98)	0.86 (0.76, 0.98)	0.87 (0.77, 0.99)
Rheumatic fever		0.61 (0.46, 0.81)	0.62 (0.46, 0.82)	0.62 (0.46, 0.84)
Knee height				1.06 (0.93, 1.21)
Father no education				0.90 (0.80, 1.02)
Father in agriculture				1.03 (0.91, 1.16)
Adult Risk				
Obesity				0.79 (0.70, 0.89)
Diabetes				0.82 (0.73, 0.92)
Ever smoked				0.94 (0.83, 1.06)
Exercises				1.09 (0.97, 1.23)
Primary education				1.00 (0.89, 1.14)
Gamma	0.42 (0.38, 0.47)	0.42 (0.37, 0.47)	0.42 (0.37, 0.47)	0.41 (0.37, 0.46)
Log-Likelihood	–742	–738	–733	–715
Number of Observations	1,438	1,438	1,438	1,438

Source: PREHCO imputed (n = 1,438 from full sample of 4,293); 60- to 74-year-olds who were born in Puerto Rico and lived in the countryside before age 18. The broad exposure period is July–December, and the level of exposure is based on the overlap between the third trimester of pregnancy and the lean harvest season: full exposure (fourth quarter), partial exposure (first quarter or third quarter), and no exposure (second quarter).

Notes: Numbers shown in the table are time ratios; 95% confidence intervals are in parentheses.

Figure 4. Predicted Hazard by Level of Exposure During Late Gestation



Source: PREHCO imputed (n = 1,438); 60- to 74-year-olds who were born in Puerto Rico and lived in the countryside as a child.

effects were largely unchanged when these variables were combined into one age- and sex-adjusted model (TR 0.79, 95% CI: 0.68, 0.93; TR 0.86, 95% CI: 0.76, 0.98; TR 0.62, 95% CI: 0.46, 0.82) (Table 3, Model 3). Similar results were obtained when a model with all covariates was estimated (Table 3, Model 4). Being born with full exposure (fourth quarter), poor childhood health, rheumatic fever, obesity, and diabetes "sped up" the time of onset of heart disease, with the strongest effect observed for rheumatic fever. The (expected) median time for onset of heart disease for those born with full exposure (fourth quarter) was about 0.80 times that of the median time to diagnosis for unexposed persons (second quarter). Tests for the adequacy of this model suggest that it successfully captures empirical patterns.[3] The effects of seasonality on heart disease were not statistically significant for respondents living in urban areas during childhood (n = 1,128; results not shown).

Given that both the Cox and log logistic models produced similar fit with the data, it is not surprising that predicted hazards and cumulative hazards from each were very similar, although the log logistic model tended to produce greater hazards at older ages (Figure 4). At older ages, the hazard doubled for full exposure (fourth quarter) in contrast with unexposed persons (second quarter). Hazards of partial exposure appeared closer to that of full exposure.

The median age at onset of heart disease varied slightly across seasons of birth (Table 4), but these differences were not statistically significant. However, there were important

3. A linear regression of Cox-Snell residuals on the Nelson-Aalen estimator hazard estimates produced an R^2 of .98 with slope close to 1 (1.18) and with y-intercept close to 0 (–0.03). The fit was very similar to that obtained with a simpler Cox model. An additional test using the Nelson-Aalen estimate of the cumulated hazard again suggested strong concordance between the model and the empirical data (results not shown).

Table 4. Median Age at Onset of Heart Disease and Ever Experienced Heart Disease Across Level of Exposure During Late Gestation: Puerto Ricans Aged 60–74, 2002–2003

	Season of Exposure During Late Gestation				
Variable	Full Exposure: Born in October–December	Partial Late Exposure: Born in January–March	Partial Early Exposure: Born in July–September	No Exposure: Born in April–June	All Exposures
Median Age at Onset of Heart Disease[a]	60	60	59	59	60
Median Age at Onset of Heart Disease[b]	60	60	58	58	60
Ever Experienced Heart Disease (%)	23	18	15	11	17

Source: PREHCO imputed and weighted (n = 1,438 from full sample of 4,293); all 60- to 74-year-olds who were born in Puerto Rico, lived in the countryside before age 18, and indicated that the onset of heart disease was at least at age 40. See Table 1 for the definition of level of exposure.

[a]The cutoff point for onset of heart disease is defined at age 40 (n = 1,438).

[b]The cutoff point for onset of heart disease is defined at age 19 or all possible ages (n = 1,456). The same results were obtained when we included childhood onset of heart disease (n = 1,459).

differences in the proportion ever experiencing heart disease: the greatest difference was between full exposure (23%) and unexposed individuals (11%), with partial exposure in between (15% and 18%). There were no statistical differences noted in median age at onset of heart disease for respondents who lived in the urban areas during childhood (n = 1,128; results not shown).

DISCUSSION

In this article, we examined whether exposure to poor nutrition and infectious diseases in utero is associated not only with the occurrence of heart disease but also with the timing of the onset of heart disease. Consistent with our expectations, the lifetime (after 60 years of age) risks of experiencing heart disease are significantly higher among those with high exposure to poor nutrition and infectious diseases during late gestation (as proxied by an indicator of season of birth) among 60- to 74-year-old Puerto Ricans. Full exposure (being born at the end of the lean season) produced risks of onset of heart disease that were 65% as high as among unexposed individuals (born at the end of the harvest season). However, there was little evidence to confirm that exposure in utero predicts or affects in any other way the timing of the onset of adult heart disease as has been suggested from other studies of the effects of early life during famine conditions (Painter et al. 2006). No associations between season of birth and heart disease materialized for those who did not live in the countryside as a child, and thus the results also corroborate earlier findings regarding the validity of season of birth as a measure of early nutrition and infectious disease exposure (McEniry et al. 2008).

Childhood health, rheumatic fever, obesity, and diabetes showed important effects on the risk and timing of the onset of heart disease and, with the exception of rheumatic fever, these effects were similar in importance to the effects of seasonal exposure. Other studies have shown the importance of these factors to adult health (Elo and Preston 1992; Haas 2007; Kuh and Ben-Shlomo 2004), but as far as we know, no other studies have examined the degree to which the effects of childhood health are attenuated when season of birth is added to model estimation. The magnitude of effects for seasonal exposure on heart disease reflects an arguably substantial impact. At the population level, however, its impact must be rather tenuous because the distribution of births by seasons is unlikely to change much

from year to year, except before or after social and economic upheavals or population crises of one sort or another. However, the results do suggest that early life exposures, at least for older Puerto Rican adults, appear to be of similar importance as these noted childhood and adult risk factors.

It is noteworthy that our results provided evidence to support the consequences of the type of fetal growth patterns suggested by the Barker hypothesis (Figure 1, pattern A) regarding the importance of early gestation in setting the path of fetal growth trajectory and creating the stage for more or less vulnerability in gestation to undernutrition. Puerto Ricans born at the end of the lean season (who have a higher risk of heart disease) would have experienced early gestation during more favorable circumstances (in the second quarter, at end of the harvest). This pattern of exposure and risk of heart disease supports the Barker idea that a more favorable nutritional environment in early gestation sets the fetus on a path of rapid growth that may cause problems if the fetus experiences severe undernutrition during late gestation (Barker 2005). Puerto Ricans born at the end of the harvest season (who have a lower risk of heart disease) would have experienced early gestation during less favorable circumstances (in the third quarter) and presumably, according to the Barker hypothesis, would have experienced slower growth and have been less affected by an undernourished late gestation. Puerto Ricans, however, most likely experienced better nutrition during late gestation (in the harvest season). This result is consistent with several studies that have indirectly shown the importance of nutrition in the third trimester and adult health status (Costa 2005*;* Doblhammer 2004; Gavrilov and Gavrilova 2005; Moore et al. 1999; Prentice and Cole 1994).

Our overall findings contradict the Dutch Famine studies (Painter et al. 2006; Roseboom et al. 2000). Several possible reasons exist for the contradictory findings:

1. Different etiologies of heart disease exist in different environments, and the physiological mechanisms related to timing in nonfamine conditions may be different than those operating with timing during conditions of famine (Godfrey and Barker 2000).

2. The relatively small sample sizes obtained in the Dutch Famine studies call into question the reliability of their findings (Huxley 2006).

3. It is also possible that the peak season for infectious diseases in Puerto Rico coincides almost perfectly with the lean season and that we were not able to clearly separate the effects of nutritional deficiencies from those that result from maternal contraction of infection or parasitic illnesses.

4. Seasonality of birth is problematic partly because it is not exact and may not coincide with the critical time for everyone, and partly because focusing exclusively on the third trimester may have missed the mark. Furthermore, it was unclear the degree to which season of birth adequately reflected conditions experienced in utero or instead was a better indicator of conditions experienced immediately after birth. The differential effects of the timing of exposure during mid- and late gestation and early infancy on adult health are largely unknown, although we know that slow growth during early infancy is associated with later heart disease (Barker et al. 2002; Eriksson et al. 2001; Osmond et al. 1993). In the case of Puerto Rico, those born toward the end of the lean season would have been fully exposed during late gestation to the lean period, but they then would have been exposed during their early infancy (the first 6–8 months) to less harsh conditions during the harvest time. The results we obtained, however, suggest that the negative effects of exposure during late gestation completely overwhelmed the beneficial effects derived from spending early infancy in times of relative slack.

5. Mortality selection in the PREHCO study may be another reason for the differences in results. However, mortality selection produces downward bias on estimated effects and thus produces conservative lower-bound estimates.

6. Even though our sensitivity analyses of different cutoff points for defining onset of heart disease produced similar results, it may be that differences in the distribution of age

at onset of heart disease and the older ages of the PREHCO sample help explain differences in the results obtained.

There are a number of additional issues that remain unresolved. The first is the degree to which the use of national-level data is appropriate to test a hypothesis that is clearly sensitive to community heterogeneity. This difficulty is of less importance in small and highly homogeneous countries such as Puerto Rico, where national and regional seasonality and economic indicators are highly consistent with each other, but it is a stumbling block otherwise. Second, there are limitations of measurement in population surveys that make it impossible to obtain precise estimates of effects. In addition to the limitations imposed by using season of birth as an indicator of exposure in utero, it is possible that self-reported time of first diagnosis for heart disease contained systematic biases, other than those generated by random noise or heaping, that were not obvious after visual inspection of the data. Self-reported chronic conditions, although underreported (Baker, Stabile, and Deri 2004; Goldman et al. 2003), have been shown to identify at least some underlying chronic conditions, including diabetes and heart disease, reasonably well (Banks et al. 2006). However, even if there were extensive underreporting of heart disease and if underreporting were unrelated to errors either in reporting of early conditions or in the date at birth, we would have been downplaying the role of season of birth and early conditions because the estimated variances of the associated coefficients would be inflated.

Despite these caveats, our findings are remarkably robust. If anything, our models overcontrolled for traits that, in theory at least, are affected by early exposure. Such is the case for height, knee height, BMI, and even diabetes. However, we found very similar results, and our inferences remained unchanged when these were excluded from model estimation. It is clear then that our estimated effects should be considered lower bounds of the true estimates and that our inferences are on the conservative side. Thus, although we found evidence for the association between a higher prevalence of heart disease and in utero conditions but did not find a case for the early onset of heart disease, our results suggest that early life conditions among this population of older Puerto Ricans had important health ramifications in their later adult years.

APPENDIX: MULTIPLE IMPUTATION

As part of the multiple imputation procedures (Raghunathan et al. 2003; Rubin 1987; Schafer 1997; Van Buren et al. 1999), we included all relevant cases, including item nonresponse as well as target individuals who were interviewed with proxies and for whom we did not have information on early conditions. The percentage of missing responses among the subsample of those born in Puerto Rico who lived in the countryside as a child was very small: less than 1% in all variables used except knee height and obesity, for which missing responses were at 3%. Missingness was higher for these variables because they required anthropometric assessments. Our primary interest, however, was the imputation of items about living in the countryside as a child and early conditions among those who required a proxy respondent and from whom no information about early conditions was elicited. These cases were important since, by definition, their health status was likely to be worse than among the rest of the sample. Finally, we were also interested in including about 8% of cases with missing age at onset of heart disease.

Thus, we imputed missingness in our variables due to either survey nonresponse or to item nonresponse with models that were suited to the outcome of interest. We adapted a Bayesian imputation approach originally proposed by Rubin (1987). These procedures require that missingness is ignorable—that is, that the pattern of missingness for each variable does not depend on the value of the missing item after conditioning on other observed variables available in the data—and that any parameters that may govern missingness are related to the parameters in our models of interest. To the extent that different types of missingness are predicted with the available data in PREHCO

(e.g., item missingness and proxy responses), our estimations for multiply imputing missingness take into account many of the observed factors that could explain missingness. This enabled us to maximize the opportunities for satisfying the assumption of ignorable missingness.

We used IVEware in SAS by Raghunathan et al. (2007). A total of five imputed data sets were determined to sufficiently capture the between-sample variance in our model estimates across multiple imputed data sets. Both categorical and continuous variables were imputed. We then selected the subsample of 60- to 74-year-old respondents from the imputed data for model estimation.

REFERENCES

Baker, M., M. Stabile, and C. Deri. 2004. "What Do Self-reported, Objective, Measures of Health Measure?" *Journal of Human Resources* 39:1067–93.

Banks, J., M. Marmot, Z. Oldfield, and J. Smith. 2006. "Disease and Disadvantage in the United States and in England." *Journal of the American Medical Association* 295:2037–45.

Barker, D.J.P. 1995. "Fetal Origins of Coronary Heart Disease." *British Medical Journal* 311:171–74.

———. 1998. *Mothers, Babies and Health in Later Life.* 2nd ed. Edinburgh, Scotland: Churchill Livingstone.

———. 2001. "The Malnourished Baby and Infant." *British Medical Bulletin* 60:69–88.

———. 2005. "The Developmental Origins of Coronary Heart Disease." Pp. 547–67 in *Coronary Heart Disease Epidemiology: From Aetiology to Public Health,* edited by M. Marmot and P. Elliott. Oxford: Oxford University Press.

Barker, D.J.P., J.G. Eriksson, T. Forsén, and C. Osmond. 2002. "Fetal Origins of Adult Disease: Strength of Effects and Biological Basis." *International Journal of Epidemiology* 31:1235–39.

Barker, D.J.P., T. Forsén, A. Uutela, C. Osmond, and J.G. Eriksson. 2001. "Size at Birth and Resilience to Effects of Poor Living Conditions in Adult Life: Longitudinal Study." *British Medical Journal* 323:1273–77.

Bengtsson, T. and M. Lindstrom. 2003. "Airborne Infectious Diseases During Infancy and Mortality in Later Life in Southern Sweden, 1766–1894." *International Journal of Epidemiology* 32:286–94.

Clark, V.S. 1930. *Porto Rico and Its Problems*. Washington, DC: The Brookings Institution.

Costa, D.L. 2005. "Becoming Oldest-Old: Evidence From Historical U.S. Data." *Genus* 61(1):125–61.

Davey Smith, G. and J. Lynch. 2004. "Life Course Approaches to Socioeconomic Differentials in Health." Pp. 77–115 in *A Life Course Approach to Chronic Disease Epidemiology,* edited by G. Davey Smith and J. Lynch. Oxford: Oxford University Press.

Doblhammer, G. 2004. *The Late Life Legacy of Very Early Life*. Berlin, Germany: Springer.

Elo, I.T. and S.H. Preston. 1992. "Effects of Early-Life Conditions on Adult Mortality: A Review." *Population Index* 58:186–212.

Eriksson, J.G., T. Forsen, J. Tuomilehto, C. Osmond, and D.J.P. Barker. 2001. "Early Growth and Coronary Heart Disease in Later Life: Longitudinal Study." *British Medical Journal* 322:949–53.

Eveleth, P.B. and J.M. Tanner. 1990. *Worldwide Variation in Human Growth*. 2nd ed. Cambridge: Cambridge University Press.

Finch, C.E. and E.M. Crimmins. 2004. "Inflammatory Exposure and Historical Changes in Human Life-Spans." *Science* 305:1736–39.

Gamble, D.R. 1980. "The Epidemiology of Insulin Dependent Diabetes, With Particular Reference to the Relationship of Virus Infection to Its Etiology." *Epidemiologic Reviews* 203(2):49–70.

Gardiner, H.M. 2007. "Early Environmental Influences on Vascular Development." *Early Human Development* 83:819–23.

Gavrilov, L.A. and N.S. Gavrilova. 2005. "Mortality of Centenarians: A Study Based on the Social Security Administration Death Master File." Paper presented at the annual meeting of the Population Association of America, March 31–April 2, Philadelphia.

Gayer, A.D., P.T. Homan, and E.K. James. 1938. *The Sugar Economy of Puerto Rico*. New York: Columbia University Press.

Gluckman, E. and M. Hanson. 2006. *Developmental Origins of Health and Disease*. Cambridge: Cambridge University Press.

Godfrey, K.M. and D.J.P. Barker. 2000. "Fetal Nutrition and Adult Disease." *American Journal of Clinical Nutrition* 71(Suppl.):1344S–52S.

Goldman, N., I. Lin, M. Weinstein, and Y. Lin. 2003. "Evaluating the Quality of Self-reports of Hypertension and Diabetes." *Journal of Clinical Epidemiology* 56:148–54.

Guerrant, R.L., A.A.M. Lima, and F. Davidson. 2000. "Micronutrients and Infection: Interactions and Implications With Enteric and Other Infections and Future Priorities." *Journal of Infectious Diseases* 182(Suppl. I):S134–S138.

Gunnell, D.J., G. Davey Smith, J.M.P. Holly, and S. Frankel. 1998. "Leg Length and Risk of Cancer in the Boyd Orr Cohort." *British Medical Journal* 317(14/11):1350–51.

Haas, S.A. 2007. "The Long-Term Effects of Poor Childhood Health." *Demography* 44:113–35.

Hertzman, C. 1994. "The Lifelong Impact of Childhood Experiences: A Population Health Perspective." *Daedalus* 123(4):167–80.

Huxley, R. 2006. "Early Nutritional Determinants of Coronary Artery Disease: A Question of Timing?" *American Journal of Clinical Nutrition* 84:271–72.

Huxley, R., A. Neil, and R. Collins. 2002. "Unraveling the Fetal Origins Hypothesis: Is There Really an Inverse Relationship Between Birth Weight and Subsequent Blood Pressure?" *Lancet* 360:659–65.

International Labor Organization. 2004. ISCO, *International Standard Classification of Occupations.* Available online at http://www.ilo.org/public/english/bureau/stat/isco/index.htm.

Joseph, K.S. and M.S. Kramer. 1996. "Review of the Evidence of Fetal and Early Childhood Antecedents of Adult Chronic Disease." *Epidemiologic Review* 18:158–74.

Kannisto, V., K. Christensen, and J.W. Vaupel. 1997. "No Increased Mortality in Later Life for Cohorts Born During Famine." *American Journal of Epidemiology* 145:987–94.

Kinsella, K. and Wan He. 2009. "An Aging World: 2008." U.S. Census Bureau, International Population Reports, P95/09-1. U.S. Government Printing Office, Washington, DC.

Klein, J.P. and M.L. Moeschberger. 1997. *Survival Analysis: Techniques for Censored and Truncated Data*. New York: Springer.

Kuh, D. and Y. Ben-Shlomo, eds. 2004. *A Life Course Approach to Chronic Disease Epidemiology.* Oxford: Oxford University Press.

Leitch, I. 1951. "Growth and Health." *British Journal of Nutrition* 5:142–51.

Lundberg, O. 1991. "Childhood Living Conditions, Health Status, and Social Mobility: A Contribution to the Health Selection Debate." *European Sociological Review* 7:149–62.

Mazumder, B., D. Almond, K. Park, E.M. Crimmins, and C.E. Finch. 2009. "Lingering Prenatal Effects of the 1918 Influenza Pandemic on Cardiovascular Disease." *Journal of Developmental Origins of Health and Disease.* Online publication (doi: 10.1017/S2040174409990031).

McEniry, M., A. Palloni, A.L. Dávila, and A. García Gurucharri. 2008. "Early Life Exposure to Poor Nutrition and Infectious Diseases and Its Effects on the Health of Older Puerto Rican Adults." *Journal of Gerontology: Social Sciences* 63B:S337–S348.

Moore, S.E., T.J. Cole, A.C. Collinson, E.M.E. Poskitt, I.A. McGregor, and A.M. Prentice. 1999. "Prenatal or Early Postnatal Events Predict Infectious Deaths in Young Adulthood in Rural Africa." *International Journal of Epidemiology* 28:1088–95.

Murray, C.J.L. and A.D. Lopez, eds. 1996. *Global Health Statistics: Global Burden of Disease and Injury Series,* Vol. II. Boston, MA: Harvard School of Public Health.

Newnham, J.P. and M.G. Ross, eds. 2009. *Early Life Origins of Human Health and Disease*. Basel, Switzerland: Karger.

Osmond, C. and D.J.P. Barker. 2000. "Fetal, Infant, and Childhood Growth Are Predictors of Coronary Heart Disease, Diabetes and Hypertension in Adult Men and Women." *Environmental Health Perspectives* 108(Suppl. 3):545–53.

Osmond, C., D.J.P. Barker, P.D. Winter, C.H.D. Fall, and S.J. Simmonds. 1993. "Early Growth and Death From Cardiovascular Disease in Women." *British Medical Journal* 307:1519–24.

Painter, R.C., S.R. de Rooij, P.M. Bossuyt, T.A. Simmer, C. Osmond, and D.J. Barker. 2006. "Early Onset of Coronary Artery Disease After Prenatal Exposure to the Dutch Famine." *American Journal of Clinical Nutrition* 84:322–27.

Palloni, A., M. McEniry, A.L. Dávila, and A. García Gurucharri. 2005. "The Influence of Early Conditions on Health Status Among Elderly Puerto Ricans." *Social Biology* 52(3/4):132–64.

Prentice, A.M. and T.J. Cole. 1994. "Seasonal Changes in Growth and Energy Status in the Third World." *Proceedings of the Nutrition Society* 53:509–19.

Puerto Rican Elderly: Health Conditions (PREHCO). 2007. 2002–2003 *Proyecto PREHCO I 2002–2003 Informe Metodológico* [Methods report, PREHCO I Project 2002–2003]. Madison, WI: University of Wisconsin, Center for Demography and Ecology; and University of Puerto Rico, Graduate School of Public Health. Available online at http://www.ssc.wisc.edu/cdha/projects/projects.html and http://prehco.rcm.upr.edu/docs/infor_met2.pdf.

Raghunathan, T.E., J.P. Reiter, and D.B. Rubin. 2003. "Multiple Imputation for Disclosure Limitation." *Journal of Official Statistics* 19:1–16.

Raghunathan, T.E., P.W. Solenberger, and J. Van Hoewyk. 2007. *IVEware: Imputation and Variance Estimation* [Computer software]. Available online at http://www.isr.umich.edu/src/smp/ive.

Ravelli, A.C.J., J.H.P. van der Meulen, R.P.J. Michels, C. Osmond, D.J.P. Barker, C.N. Hales, and O.P. Bleker. 1998. "Glucose Tolerance in Adults After Prenatal Exposure to the Dutch Famine." *Lancet* 351:173–77.

Rigau Pérez, J.G. 2000. "La Salud en Puerto Rico en el Siglo XX" [Health in Puerto Rico in the twentieth century]. *Puerto Rican Health Sciences Journal* 19:357–68.

Roseboom, T.J., J.H.P. van der Meulen, C. Osmond, D.J.P. Barker, A.C.J. Ravelli, J.M. Schroeder-Tanka, G.A. van Montfrans, R.P.J. Michels, and O.P. Bleker. 2000. "Coronary Heart Disease After Prenatal Exposure to the Dutch Famine, 1944–45." *Heart* 84:595–98.

Rubin, D. 1987. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons.

Schafer, J.L. 1997. *Analysis of Incomplete Multivariate Data*. London: Chapman & Hall.

Scrimshaw, N.S. 1968. *Interaction of Nutrition and Infection*. New York: World Health Organization.

———. 1997. "Nutrition and Health From Womb to Tomb." *Food and Nutrition Bulletin* 18(1):1–19.

Simondon, K.B., E. Elguero, A. Marra, A. Diallo, P. Aaby, and F. Simondon. 2004. "Quarter of Birth Is Not Associated with Risk of Early Adult Death in Rural Senegal." *International Journal of Epidemiology* 33:130–36.

Stanner, S.A., K. Bulmer, C. Andrès, O.E. Lantseva, V. Borodina, V.V. Poteen, and J.S. Yudkin. 1997. "Does Malnutrition in Utero Determine Diabetes and Coronary Heart Disease in Adulthood? Results From the Leningrad Siege Study, a Cross Sectional Study." *British Medical Journal* 315:1342–48.

Van Buren, S., H.C. Boshuizen, and D.L. Knook. 1999. "Multiple Imputation of Missing Blood Pressure Covariates in Survival Analysis." *Statistics in Medicine* 18:681–94.

Wadsworth, M.E. and D.J. Kuh. 1997. "Childhood Influences on Adult Health: A Review of Recent Work From the British 1946 National Birth Cohort Study, the MRC National Survey of Health and Development." *Paediatric and Perinatal Epidemiology* 11:2–20.